PATENT SPECIFICATION

1,024,908

NO DRAWINGS

1,024,908

Inventor: JOSEPH PATRICK BROWN

Date of filing Complete Specification: Sept. 10, 1964.

Application Date: Nov. 4, 1963. No. 43515/63.

Complete Specification Published: April 6, 1966.

Index at acceptance:—C2 C(1F2A2, 1F2C4, 1F2C5, 1F2D3, 1H1A2, 1H1C3, 2A3, 2A7, 2A12, 2B3A4, 2B3B, 2B3D, 2B3E, 2B3F, 2B3G5, 2B3G7, 2B3G8, 2B3G9, 2B44D1, 2B44G2, 2R16, 2R18, 2R20)

Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

Pyrimidine Derivatives

We, MONSANTO CHEMICALS LIMITED, a British Company, of Monsanto House, 10—18, Victoria Street, London, S.W.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

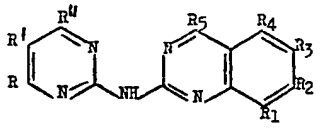
This invention relates to pyrimidine derivatives, more particularly to new compounds containing both a pyrimidine and a quinazoline nucleus.

The compounds are in fact 2(quinazol-2′-ylamino)pyrimidines. They have microbiocidal and antioxidant properties, and they are useful as intermediates in the production of pharmaceuticals, for instance materials for the treatment of parasitic diseases, in particular protozoal diseases. They are also intermediates in the production of dyestuffs.

The invention also includes a process for the production of a new 2(quinazol-2′-ylamino)pyrimidine, in which a 2-guanidinoquinazoline is reacted with a compound that forms a pyrimidine ring by cyclisation with the guanidino group of the 2-guanidinoquinazoline.

Such compounds include those containing a β-dicarbonyl system, for example acetylacetone or acetoacetic ester, compounds containing a β-cyanocarbonyl system, for example cyanoacetic ester, and compounds containing a β-dicyano system, for example malononitrile.

The new 2(quinazol-2′-ylamino)pyrimidines include compounds having the formula:



where R and R″ are each a hydrogen atom, an amino group, a hydroxyl group, an aromatic group, or a group A, A being aliphatic, alicyclic or aralkyl; R′ is a hydrogen or halogen atom, an acylamino group, a group A, a group AO—, or an aromatic group; R_1, R_2, R_3 and R_4 are each a hydrogen or halogen atom, a group A, a group AO—, or an aromatic group; and R_5 is a hydrogen atom or an alkyl group.

In most instances, not more than two of R_1, R_2, R_3 and R_4 represent atoms or groups other than hydrogen, and the remainder represent hydrogen.

Where R or R″ is a group A, it can be for example an alkyl group, a cycloalkyl group or an aralkyl group, or one of these groups carrying a substituent, for example a halogen atom or an alkoxy group. An aromatic group R or R″ can be for example an aryl or substituted aryl group.

Of the compounds in which R or R″ represents an alkyl group, those where the alkyl group is one containing up to four carbon atoms, and particularly those where it is a methyl or ethyl group, are often the most readily accessible. R or R″ can however represent a higher alkyl group, for example a hexyl, nonyl or dodecyl group.

Cycloalkyl groups from which R or R″ can be selected include for instance cyclopentyl and cyclohexyl. Where R or R″ is an aralkyl group, it can be for example a benzyl or phenylethyl group, and where either is an aromatic group, it can be for example a phenyl or chlorophenyl group.

Where R′ is a group A or an aromatic group, it can in general be selected from the same range of such groups as the substituents R and R″ discussed above.

The portion A or a group AO— can also be selected from the same range of groups A as the groups R and R″. AO—can thus for example represent a methoxy, butoxy, cyclohexyloxy or benzyloxy group.

Where R′ represents a halogen atom, the

[*Price 4s. 6d.*]

halogen is usually chlorine or bromine, and where R′ represents an acylamino group, this can be for example an acetylamino or propionylamino group.

Because of the availability of the starting materials, the 2(quinazol-2′-ylamino)pyrimidines where R′ in the above formula is hydrogen are generally the most readily obtainable.

Referring to the substituents R_1, R_2, R_3 and R_4, where one of these represents a halogen atom, the halogen is most commonly chlorine or bromine, but it can be fluorine or iodine.

Where R_2, R_3, R_4 and R_5 is a group A, this can be for instance an alkyl group, an alkenyl group, a cycloalkyl group or an aralkyl group, and correspondingly a group AO— can be one where an alkyl, alkenyl, cycloalkyl or aralkyl group is linked to the quinazoline nucleus through an oxygen atom. An alkyl group (and the alkyl portion of an alkoxy group) can have a straight or branched chain and in most instances is one containing up to about 20 carbon atoms. Typical alkyl groups are methyl, ethyl, isopropyl, t-butyl, 2,2,4 - trimethylpentyl, n-dodecyl and n-octadecyl. Typical alkoxy groups are methoxy, ethoxy, n-propoxy, n-amyloxy, 2-ethylhexyloxy, and n-decyloxy.

Examples of other groups A and AO— from which R′ and R_1 to R_5 can be selected are allyl, allyloxy, cyclopentyloxy, cyclohexyl, cyclohexyloxy, benzyl and benzyloxy.

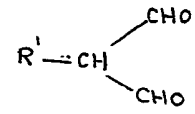
Where one of R_1 to R_5 represents an aromatic group, this is generally an aryl or substituted aryl group, for example a phenyl or substituted phenyl group such as for instance a chlorophenyl or alkoxyphenyl group.

Referring to R_5, the most accessible 2(quinazol - 2′ - ylamino)pyrimidines are in general those where R_5 represents a methyl group, but R_5 can be a hydrogen atom or an alkyl group containing two or more carbon atoms, particularly one containing two to four carbon atoms, that is to say, an ethyl, propyl or butyl group.

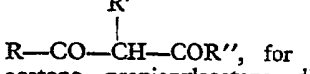
Specific examples of the new 2(quinazol-2′-ylamino)pyrimidines are:

2(4′ - methylquinazol - 2′ - ylamino)-pyrimidine; 5 - chloro - 2(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4,6 - dimethyl-2(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4,6 - dimethyl - 2(6′ - methylquinazol-2′ - ylamino)pyrimidine; 4,6 - dimethyl - 2-(6′ - t - butyl - 4′ - methylquinazol - 2′-ylamino)pyrimidine; 4,6 - dimethyl - 2(6′-chloro - 4′ - methylquinazol - 2′ - ylamino)-pyrimidine; 4,6 - dimethyl - 2(6′ - ethoxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4,6 - dimethyl 2(7′ - chloro - 6′ - ethoxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4,6 - dimethyl - 2(6′ - benzyloxy - 4′ - methylquinazol - 2 - ylamino)pyrimidine; 4,6-diethyl - 2(4′ - methylquinazol - 2′ - ylamino)-pyrimidine; 4 - cyclohexyl - 6 - methyl - 2(4′-methylquinazol - 2′ - ylamino)pyrimidine; 4,6 - dibenzyl - 2(4′ - methylquinazol - 2′-ylamino)pyrimidine; 4,6 - diphenyl - 2(4′-methylquinazol - 2′ - ylamino)pyrimidine; 4,5,6 - trimethyl - 2(4′ - methylquinazol - 2′-ylamino)pyrimidine; 4 - hydroxy - 2(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4-hydroxy - 6 - methyl - 2(quinazol - 2′-ylamino)pyrimidine; 4 - hydroxy - 6 - methyl-2(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4 - hydroxy - 6 - methyl - 2(6′ - ethoxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4 - hydroxy - 6 - methyl - 2(6′ - allyloxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4 - hydroxy - 6 - methyl - 2(6′ - decyloxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4 - hydroxy - 6 - methyl - 2(6′ - bromo - 4′-methylquinazol - 2′ - ylamino)pyrimidine; 5 - ethyl - 4 - hydroxy - 6 - methyl - 2(4¹-methylquinazol - 2¹ - ylamino)pyrimidine; 5 - ethoxy - 4 - hydroxy - 6 - methyl - 2(4′-methylquinazol - 2′ - ylamino)pyrimidine; 4 - hydroxy - 6 - n - butyl - 2(4¹ - methylquinazol - 2′ - ylamino)pyrimidine; 4,6-dihydroxy - 2(4′ - methylquinazol - 2′-ylamino)pyrimidine; 4,6 - dihydroxy - 2(6′-ethoxy - 4′ - methylquinazol - 2′ - ylamino)-pyrimidine; 5 - acetylamino - 4,6 - dihydroxy-2(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 5 - benzyl - 4,6 - dihydroxy - 2(4′-methylquinazol - 2′ - ylamino)pyrimidine; 5 - methoxy - 4,6 - dihydroxy - 2(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4 - amino-6 - methyl - 2(4 - methylquinazol - 2′-ylamino)pyrimidine; 4 - amino - 6 - hydroxy-(4′ - methylquinazol - 2′ - ylamino)pyrimidine; 4 - amino - 6 - hydroxy - 2(6′ - ethoxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine; and 4,6 - diamino - 2(4′ - methylquinazol -2′-ylamino)pyrimidine.

In the process for the production of a new 2(quinazol-2′-ylamino)pyrimidine, the choice of starting materials is of course determined by the particular product required. Where R and R″ in the formula above are both hydrogen, the compound that is reacted with the 2-guanidinoquinazoline is a malondialdehyde having the formula



for example malondialdehyde itself, ethylmalonialdehyde itself, ethylmalondialdehyde or chloromalondialdehyde. Where R and R″ are both aliphatic or aromatic groups, the compound is a β-diketone of formula

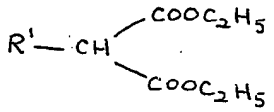


for example acetylacetone, propionylacetone, dibenzoylmethane, 3 - methylpentane - 2,4 - dione or 3-phenylpentane-2,4-dione.

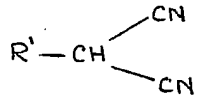
A β-ketoester, for instance a β-keto ethyl ester having the formula

$$RCOCH(R')—COOC_2H_5,$$

is employed where the required product is one in which R is an aliphatic or aromatic group and R'' is a hydroxy group. Examples of such β-ketoesters are ethyl acetoacetate, ethyl β-acetopropionate, and ethyl benzoylaceate. A malonic diester, for example a diethyl malonate of formula



such as for instance diethyl malonate, diethyl methylmalonate, diethyl cyclohexylmalonate, diethyl ethoxymalonate and diethyl acetylaminomalonate, gives a 2(quinazol-2'-ylamino)-pyrimidine in which both R and R'' are hydroxy groups; a cyanoacetic ester, for example an ethyl cyanoacetate of formula $NC.CH(R')—COOC_2H_5$, such as for instance ethyl cyanoacetate itself and ethyl α-cyanobutyrate, gives a 2(quinazol - 2' - ylamino)-pyrimidine in which R is a hydroxy group and R'' is an amino group; and a malonitrile of formula



such as for instance malononitrile itself and benzylmalononitrile, gives a 2(quinazol-2'-ylamino)pyrimidine in which both R and R'' are amino groups.

The guanidinoquinazoline starting material is one in which the substituents, if any, that are required in the quinazoline nucleus of the product (that is to say, in the instance of the 2(quinazol-2'-ylamino)pyrimidines having the formula above, those represented by R_1 to R_5) are already present. These play no part in the molecular transformation involved in the process. The guanidinoquinazoline can for instance be any of those described in our British Patent Specification 900,779 that contains a 2-guanidino group

$$—NH—C(:NH)NH_2.$$

Some of the guanidinoquinazolines so described are claimed in the said specification as new compounds.

For a practical reaction rate between the guanidinoquinazoline and the compound that forms a pyrimidine ring by cyclisation with the guanidino group of the guanidinoquinazoline, it is usually necessary to heat the reactants to an elevated temperature, for example a temperature of at least 50°C, and preferably at a temperature within the range 100—200°C, for example at about 150°C.

The reaction can be carried out in an inert solvent, for example ethanol, ethoxyethanol or dimethylformamide, although this is not essential. Where, as is often the case, the compound that reacts with the guanidinoquinazoline is a liquid at the reaction temperature, this material, used in excess of the stoichiometric amount, can also function as a solvent. The use of a solvent having a boiling point at atmospheric pressure within the required reaction temperature range is often a convenient method of controlling the reaction temperature, since the process can then be conducted by boiling under reflux. The process can however be carried out at elevated pressure, either with or without a solvent, if this is necessary to achieve the desired reaction temperature.

Where the compound that reacts with the guanidinoquinazoline is a solvent in the process, the amount used is, as indicated above, in excess of the amount required to react with the guanidinoquinazoline, and may be several times this amount. Otherwise, for example where an inert solvent is employed, substantially equivalent amounts of the two reactants are generally used.

The invention is illustrated by the following Examples.

EXAMPLE 1

This Example describes the production of 4,6 - dimethyl - 2(4' - methylquinazol - 2'-ylamino)pyrimidine from 2 - guanidino - 4-methylquinazoline and acetylacetone.

A mixture of 12 grams of powdered 2 - guanidino - 4 - methylquinazoline and 60cc. of acetylacetone was boiled under reflux for 2 hours. Excess acetylacetone was then distilled off under reduced pressure, and on standing, the residue slowly solidified. Trituration of the solid with ethanol yielded 11.2 grams of 4,6 - dimethyl - 2(4' - methylquinazol - 2' - ylamino)pyrimidine as an off-white solid having a melting point of 134—135°C. The melting point was unchanged after crystallisation of the product from ethanol. (Found: C, 67.9; H, 5.9; N, 26.2. $C_{13}H_{15}N_5$ requires C, 67.9; H, 5.7; N, 26.4%)

EXAMPLE 2

This Example describes the production of 4,6 - dimethyl - 2(6' - ethoxy - 4' - methylquinazol - 2' - ylamino)pyrimidine from 6-ethoxy - 2 - guanidino - 4 - methylquinazoline and acetylacetone.

A mixture of 12 grams of powdered 6-ethoxy - 2 - guanidino - 4 - methylquinazoline and 60cc. of acetylacetone was boiled under

reflux for 2 hours. On cooling, 11 grams of 4,6 - dimethyl - 2(6′ - ethoxy - 4′ - methylquinazol - 2′ - ylamino)pyrimidine separated from the reaction mixture in the form of pale yellow plates having a melting point of 210—212°C. Recrystallisation from ethanol raised the melting point to 212—213°C. (Found: C, 66.9; H, 6.3. $C_{17}H_{19}N_5O$ requires C, 66.0; H, 6.1%)

EXAMPLE 3

This Example describes the production of 4 - hydroxy - 6 - methyl - 2(4′ - methylquinazol - 2′ - ylamino)pyrimidine from 2-guanidino - 4 - methylquinazoline and ethyl acetoacetate.

A solution of 4 grams of 2-guanidino-4-methylquinazoline and 2.6 cc. of ethyl acetoacetate in 50 cc. of 2-ethoxycthanol was boiled for 30 minutes. After cooling and standing overnight, 1.5 grams of 4 - hydroxy - 6-methyl - 2(4′ - methylquinazol - 2′ - ylamino)-pyrimidine in the form of buff-coloured plates having a melting point of 285—290°C had separated and were filtered off. The product was soluble in both aqueous acid and aqueous alkali solutions. (Found: C, 62.6; H, 4.9 $C_{13}H_{11}N_5O$ requires C, 61.8; H, 4.5%)

In a preparation in the absence of solvent, 4 grams of 2-guanidino-4-methylquinazoline and 10 cc. of ethyl acetoacetate were heated together, the ethanol formed during the reaction being distilled off continuously so that the temperature rose to 210°C. during 30 minutes. After cooling, the product was boiled with 30 cc. of ethanol for 30 minutes. The mixture was cooled and then filtered, giving 4.6 grams of solid product having a melting point of 280—284°C.

EXAMPLE 4

This Example describes the production of 4,6 - dihydroxy - 2(6′ - ethoxy - 4′ - methylquinazol - 2′ - ylamino)pyrimidine from 6-ethoxy - 2 - guanidino - 4 - methylquinazoline and diethyl malonate.

A mixture of 10 grams of 6-ethoxy-2-guanidino-4-methylquinazoline and 17 cc. of diethyl malonate was stirred and heated under reflux. At 110°C, practically all the solid was in solution, and on continued heating the temperature of the solution rose to 143°C. after 10 minutes. Solid then began to separate, and heating was discontinued. After cooling, 30 cc. of ethanol and 100 cc. of acetone were added, giving a suspension from which 9.3 grams of crude 4,6 - dihydroxy - 2(6′ - ethoxy-4′ - methylquinazol - 2′ - ylamino)pyrimidine was isolated by filtration. After drying, the product was purified by digestion with 100 cc. of boiling acetone, and was then obtained as 8.3 grams of a light-brown powder having a melting point (with decomposition) of 302°C.

EXAMPLE 5

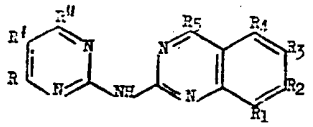
This Example describes the production of 4 - amino - 6 - hydroxy - 2(6′ - ethoxy - 4′-methylquinazol - 2′ - ylamino)pyrimidine from 6 - ethoxy - 2 - guanidino - 4 - methylquinazoline and ethyl cyanoacetate.

A mixture of 10 grams of 6-ethoxy-2-guanidino-4-methylquinazoline and 30 cc. of ethyl cyanoacetate was heated with stirring and removal of the ethanol of reaction. Practically all the solid had dissolved at 120°C., but fresh solid separated as the temperatures rose, and heating was discontinued at 250°C. After cooling, 30 cc. of ethanol were added giving a suspension from which 8.4 grams of 4 - amino - 6 - hydroxy - 2(6′ - ethoxy - 4′-methylquinazol - 2′ - ylamino)pyrimidine were isolated by filtration. The product had a melting point (with decomposition) of about 320°C.

WHAT WE CLAIM IS:—

1. A 2(quinazol-2′-ylamino) pyrimidine.

2. A 2(quinazol-2′-ylamino) pyrimidine having the formula:



where R and R″ are each a hydrogen atom, an amino group, a hydroxyl group, an aromatic group, or a group A, A being aliphatic, alicyclic or aralkyl; R′ is a hydrogen or halogen atom, an acylamino group, a group A, a group AO—, or an aromatic group; R_1, R_2, R_3 and R_4 are each a hydrogen or halogen atom, a group A, a group AO—, or an aromatic group; and R_5 is a hydrogen atom or an alkyl group.

3. A 2(quinazol-2′-ylamino) pyrimidine acording to Claim 2, in which when R or R″ is an aliphatic group this is an alkyl group containing up to four carbon atoms.

4. A 2(quinazol-2′-ylamino) pyrimidine according to either of Claims 2 and 3, in which not more than two of R_1, R_2, R_3 and R_4 represent atoms or groups other than hydrogen and the remainder represent hydrogen.

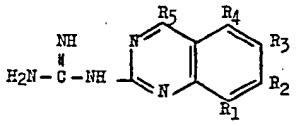
5. A 2(quinazol-2′-ylamino) pyrimidine according to any of Claims 2 to 4, in which when R_5 is an alkyl group this is one containing up to four carbon atoms.

6. A 2(quinazol-2′-ylamino) pyrimidine according to Claim 5, in which R_5 is a methyl group.

7. A 2(quinazol-2′-ylamino) pyrimidine substantially as described in any of Examples 1 to 5.

8. A process for the production of a 2(quinazol-2′-ylamino)pyrimidine, in which a 2-guanidinoquinazoline is reacted with a compound that froms a pyrimidine ring by cyclisation with the guanidino group of the 2-guanidinoquinazoline.

9. A process according to Claim 8 for the production of a 2(quinazol-2′-ylamino) pyrimidine as defined in any of Claims 2 to 6, in which the 2-guanidinoquinazoline has the formula:



where R_1 to R_5 have the same significance as in the 2(quinazol-2′-ylamino) pyrimidine, and the compound that cyclises with the guanidino group is one that is appropriate to provide the required atoms or groups represented by R, R′ and R″.

10. A process for the production of a 2(quinazol-2′-ylamino)pyrimidine substantially as described in any of Examples 1 to 5.

11. A 2(quinazol-2′-ylamino) pyrimidine that has been obtained by a process according to any of Claims 8 to 10.

C. G. WICKHAM,
Chartered Patent Agent,
Monsanto Chemicals Limited,
Monsanto House, 10—18, Victoria Street,
London, S.W.1.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.